Remarks

Reconsideration is respectfully requested in view of the above amendments and following remarks. Revisions to claims are supported, for instance, at page, lines. Claims 1-16 are pending.

Claim 6 is objected to for informalities. As suggested, revisions have been made to claim 6. Applicants respectfully submit claim 6 now is in proper form.

Reconsideration is respectfully requested.

Claims 1-4, 6-11, and 13-16 are rejected as being indefinite. Applicants respectfully traverse this rejection, and respectfully request reconsideration in view of the following comments.

Claims 1 and 14 recite 2 to 6 antibodies, each conjugated to a particle, are incubated. Therefore, 2-6 antibodies each conjugated to a particle are used.

Further, claims 1 and 14 recite the ratio between the number of particles and the number of cells in the cell suspension ranging from 0.5 : 1 to 20 : 1. The figure 0.5 is not in reference to an actual number of particles bound to a cell, such as a half particle for every cell. However, the ratio is in reference to a relationship of 1 particle bound to two cells.

With respect to the ranges "2-6" and "0.01μm -6μm", they have been revised, as suggested.

In claim 6, the language "associated" has been removed. Further, the notation MW has been incorporated for consistency, as suggested.

In addition, claims 6, 8, 11, and 13 are indefinite for reciting cancer antigens, where claim 1, which claims 6, 8, 11, and 13 depend upon, specifically excludes malignant target cells. It is respectfully submitted that claim 1 excludes both malignant hematopoietic and lymphatic cells and normal hematopoietic and lymphatic cells. However, claim 1 does not exclude all malignant cell targets. Therefore, recitations of cancer antigens in the above claims are definite.

Claim 13 has been edited, where "par human epitope" has been changed to "pan human epitope" to correct typographical error. Further, the dependency of claim 13 has been corrected to depend from claim 10. The term "the biologically informative markers" has been revised to "biological markers", and should have proper antecedent basis.

With the above revisions, it is respectfully submitted that the claims now are definite. Withdrawal of the rejection, and favorable consideration is respectfully requested.

Claim 7 is rejected under 35 U.S.C. 112, fourth paragraph, for not further limiting the subject matter of the preceding claim. Applicants respectfully traverse this rejection, and respectfully request reconsideration in view of the following comments.

Claim 7 depends upon claim 1. Claim 7 recites the antigenic determinants/receptors expressed on the target cells are tumor antigens. Claim 7 further limits the antigenic determinants/receptors to include that the particle antibody conjugate is also directed against antigenic determinants/receptors being tumor antigens. It is respectfully submitted that claim 7 further limits the subject matter of claim 1.

Favorable consideration is respectfully requested.

Claims 1-4, 6-11, and 13-14 are rejected under 35 U.S.C. 112, first paragraph, for lack of enablement. Applicants respectfully traverse this rejection, and respectfully request reconsideration in view of the following comments.

The claims are directed to particles coated with antibodies directed against antigenic determinants/receptors expressed on target cells. Applicants respectfully assert that the specification provides adequate enbablement for the claimed invention. Table 1 provides a list of specific antigens and their corresponding antibodies that can be used in the claimed method according to the relevant object of study. In addition, the detailed examples in Applicants' specification provide adequate description for the implementation of the claimed invention.

Upon reading Applicants' specification, it is respectfully submitted that one would know to choose an antibody that corresponds to a known antigen expressed on a particular target cell(s) of interest. In the claimed invention, antibodies and antigens are used and selected for detection and characterization of target cells from other cells. It is well known in the art that the use of specific antibodies depends on the object of study. Further, cells have many known antigens expressed on their surface, and the choice of antibody depends on the situation.

Therefore, one of skill in the art would understand and be able to perform the requirements as appropriate of the claimed invention without undue experimentation.

Favorable consideration is respectfully requested.

Claims 1, 6-8, 11, 13, and 14-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Fodstad et al. Applicants respectfully traverse this rejection, and respectfully requests reconsideration in view of the following comments.

Fodstad discloses methods directed to antibodies incubated with particles and antibody coated particles incubated with free antibodies. Further, the prelabelled antibody of Fodstad is labelled with small fluorescent molecules and tags, such as fluorescent agents, metallocolloids, and radioisotopes. Claims 1 and 14 recite methods where fluorescent or dyed particles are coated with antibodies. However, the cited reference does not teach or suggest fluorescent particles with the sizes described in the claimed invention coated with non-labelled antibodies.

Therefore, as the particle is a fluorescent or dyed particle, the claimed invention uses different particle and antibody coated complex. Accordingly, the cited reference does not anticipate the claimed invention.

Furthermore, the claimed invention is not obvious. As recited in the claims, the particle itself is fluoresent or dyed, and a fluorescent tag is not used. The method of Fodstad would not reasonably arrive at the claimed invention. The cited reference uses fluorescent tags for labelling antibodies, which would not be of suitable size. The claimed invention provides the advantage of a larger fluorescent or dyed particle, and due to the size of the particle, enjoys fluorescent strength for a considerable amount of time. Therefore, it is respectfully submitted the claimed invention is patentable over the cited reference for at least the above-identified reasons.

Withdrawal of the rejection and favorable consideration are respectfully requested.

Claims 1-4, 6-11, 13-14, and 15-16 are rejected under 35 U.S.C. 103(a) as being obvious over Hajek et al. in view of Fodstad et al. and O'Briant et al. Applicants respectfully traverse this rejection, and respectfully request reconsideration in view of the following comments.

Hajek et al. is directed to cells combined with one or more different sets of microspheres, where the cells and microspheres are formed as a smear on a slide and stained with a histological type stain. Further, the cited reference discloses fluorescent-tagged antibody. The claimed invention recites 14 recite methods where fluorescent or dyed particles are coated with antibodies. However, Hajek et al. does not teach or suggest fluorescent or dyed particles with the sizes described in the claimed invention coated with non-labelled antibodies. In addition, the claimed invention is directed to cells in suspension, and not cells formed as smears and stained as in the cited reference.

Fodstad et al. is distinguished from the claimed invention above. Therefore, for at least the reasons discussed above, Fodstad et al. does not remedy the deficiencies of Hajek et al.

O'Briant et al. does not teach or suggest fluorescent or dyed particles as in the claimed invention. Therefore, O'Briant et al. also does not overcome the deficiencies of Hajek et al.

Accordingly, the cited references either alone or in combination, do not reasonably arrive at the claimed invention. It is respectfully submitted that the claims are patentable over the cited references for at least the reasons discussed above.

Withdrawal of the rejection is respectfully requested.

Conclusion

With the above amendments and remarks, Applicants believe that the claims now pending in this patent application are in a condition for allowance. Favorable consideration is respectfully requested. If any further questions arise, the Examiner is invited to contact Applicants' representative at the number listed below.

Respectfully submitted,

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Mark up copy of Application Serial No. 09/331,376.

1. (Amended) Method to detect and phenotype target cells in cell suspensions by using particles coated with antibodies directed against antigenic determinants/receptors expressed on the target cells, except when the target cells are malignant and normal haematopoietic and lymphatic cells, wherein 2 to 6 antibodies, each conjugated to a particle, wherein the particle is a fluorescent or dyed particle, are incubated under gentle rotation for about 5 minutes to about 2 hours with cell suspensions containing the target cells at 0°C to 25°C, [optionally] followed by an enrichment procedure, and evaluation of the target cell rosettes microscopically and/or by suitable visualizing or imaging devices, and wherein one antibody is conjugated to one type of particle instrumentally or visually separable by fluorescence, color and size, with sizes of the particles ranging from 0.01μm [-] to 6μm, each antibody of the 2 [-] to 6 antibodies is conjugated to different particles, and the ratio between the number of particles and the number of cells ranges from 0.5 : 1 to 20 : 1 in the cell suspension.

6. (Amended) Method according to claim 7, wherein the particles used in the method are coated with antibodies directed against the receptors/antigens selected from the group consisting of integrins, ICAM-1 (CD54), VCAM-1, NCAM (CD56), HCAM, LCAM, CD44, CD44 variants, ELAM-1, E-selectin, P-selectin, LFA (CD58), MACAN-1, E-cadherin, P-cadherin, tenascin, thrombospondin receptor (CD36), VLA-2, T-antigen, Tn-antigen, sialyl Tn, galbl-4GlcNac (nL4, 6, 8), gastrointestinal cancer [associated] antigen, Le^y, di-Le^x, tri Le^x, CA15-3 epitope, CEA, lacto-N-fucopentanose III (CD15), GD_3, GD_2, Gb_3, GM_3, GM_2, $FucGM_1$, EGF receptor, c-erbB-2 (HER2), PDGFα receptor, PDGFβ receptor, transferrin receptor, NGF receptor, IL-2 receptor (CD25), c-kit, TNF receptor, high molecular weight melanoma antigen (HMW 250,000), [Mw] MW 105 [melanomia-associated] melanoma glycoprotein, MW100 kDa antigen (melanoma/carcinoma), gp 113, p95-100, gp75/TRP-1, gp 100-107, MAA, [M] MW125kD (gp125), MAGE 1, MAGE 2, MAGE 3, tyrosinase, TP-1 epitope, Tp-3 epitope, [M.] MW 200kD sarcoma antigen, [M.] MW160kD sarcoma antigen, EGP-2 (cluster 2 epithelial antigen), MUC-1 antigens, MUC-2, MUC-3, LUBCRU-G7 epitope (gp 230kD), prostate specific antigen, prostate cancer antigen, prostate high molecular antigen ([M.] MW>400kD),

polymorphic epithelial mucins, prostate specific membrane antigen (Cyt-356), human milk fat globin, 42kD breast carcinoma epitope, [Mw] MW > 10^6 mucin, ovarian carcinoma OC125 epitope ([m.] MW 750 kD), pancreatic HMW [glycoptotein] glycoprotein, colon antigen Co-17-1A ([M.] MW 37000), Ga 733.2, TAG 72, pancreatic cancer [associated] marker, pancarcinoma marker, prostrate adenopcarcinoma-antigen, [Mw] MW 150-130kD adenocarcinoma marker, [Mw] MW 92kD bladder carcinoma marker, [Mw] MW 600kD bladder carcinoma marker, bladder carcinoma antigen, hepatocellular carcinoma antigen, [Mw] MW 48kD colorectal carcinoma marker, colon specific antigen, lung carcinoma antigen [M.] MW 350-420kD, colon cancer[-associated] marker, bladder carcinoma antigens, neuroblastoma[-associated] epitope, Mel-14 epitope, HMW 250kD glioma antigen, [M.] MW 18-22kD head and neck cancer antigen, HLA Class 1 antigen, HLA-A, HLA-B, HLA-A2, HLA-ABC, HLA-DR, HLA-DQ, HLA-DP, β2-microglobulin, Fas (CD95/APO-1), FAsL, P75, cathepsin D, neuroglandular antigen (CD63), pan-human cell antigen, motility related antigens, proliferation[-associated] markers, differentiation[-associated] markers, [drud] drug resistance-related [marlkers] markers, angiogenesis[-associated] markers, chemokine receptor markers, invasion-related antigens, B-cell CD antigens, and T-cell CD antigens.

7. (Amended) Method according to claim[s] 1, wherein [the particles used in the method are coated with antibodies directed to] the antigenic determinants/receptors expressed on the target cells are tumor [associated] antigens.

8. (Amended) Method according to claim 7, wherein the tumor [associated] antigens are MOC31 anti EGP2 (anti-epithelial cell marker) antibody, anti-breast mucin (MUC1) antibody (BM7), 595, anti-EGF receptor (425.3), anti-erbB2 and anti-HMW melanoma antigen (9.2.27).

10. (Amended) Method according to claim 9, wherein the target cell characteristics of [biologically informative] biological markers of diagnostic, prognostic and therapeutic value are registered.

12. (Amended) Method according to claim 10, wherein the [biologically informative] biological markers are adhesion molecules, growth factor receptors, carcinoma markers,

carbohydrate antigens, melanoma antigens, sarcoma antigens, glioma antigens, apoptosis [associated] markers, motility related markers, proliferation [associated] antigens, differentiation [associated] markers, drug resistance markers, angionesis [associated] markers chemokine receptors, invasion- related markers and other antigens.

13. (Amended) Method according to claim [1] 10, wherein the [biologically informative] biological markers are E-cadherin, EGFr, c-erbB2, IL-2 receptor, TNF receptor , EGP2, MUC1, MUC2 & 3, PSA, PSM, GA733.2, TAG72, 15-3 epitope, ovarian carcinoma CA- 125 epitope, Le^y, CEA, 15-3 epitope, HMW 250000 melanoma antigen, gp 75/TRP-1, p95, MAG 1, MAG 2, MAG 3, TP 1 and TP 3 eptiopes, Mel-14 epitope, Fas, FasL, p75, KAT-1, AMF, gp120, MUC 18, TA99, MDR, MRP, VEGFr, bFGF, CCR, CXCR, uPAR, uPA, PAI-1, TIMP1 & 2, MMP9, stromelysins, and cathepsin D and [par-human epitope] pan-human epitope.

14. (Amended) Kit to detect and phenotype target cells in cell suspensions by using particles coated with antibodies/ligands directed against antigenic determinants/receptors expressed on the target cells, except when the target cells are malignant and normal haematopoietic and lymphatic cells, wherein 2 [-] to 6 antibodies or ligands each conjugated to a particle, wherein the particle is a fluorescent or dyed particle, are incubated under gentle rotation for 5-10 minutes to 2 hours with cell suspensions containing the target cells at 0°C to 25°C, [optionally] followed by an enrichment procedure, and evaluation of the target cell rosettes microscopically and/or by suitable visualizing or imaging devices, wherein the kit comprises particles conjugated to antibodies/ligands, wherein one antibody is conjugated to one type of particle instrumentally or visually separable by fluorescence, color and size, with sizes of the particles ranging from 0.01μm [-] to 6μm, each antibody of the 2 [-] to 6 antibodies is conjugated to the same or different particles, and the ratio between the number of particles and the number of cells ranges from 0.5 : 1 to 20 : 1 in the cell suspension.